Ans: PCT AN:

PATENT SPECIFICATION

NO DRAWINGS

Inventors: HERBERT TIMMINGTON and WILFRED HERBERT LINNELL

857,194

Date of filing Complete Specification: April 1, 1958.

Application Date: July 5, 1957. *No. 21336/57.*

Complete Specification Published: Dec. 29, 1960.

Index at acceptance:—Classes **2(6)**, P7A, P7D(2A1:2A2B:3), P7K(7:8), P7T2(D:E:F:X), P8(A:D1B:K7:T2D); **and 81(1)**, B2(P:S).

International Classification:—A61k.

ERRATA

SPECIFICATION NO. 857,194

Page 2. line 64, *for* "trignelline" *read* "trigonelline"

Page 5, line 4, *before* "5-20%" *read* "A"

Page 6, line 45, *after* "either" *read* "of"

Page 7, line 115, *for* "E." *read* "E,"

Page 8, line 1, *after* "Asperin" *insert* a comma

Page 8. line 66, *for* "F.F." *read* "F.F"

THE PATENT OFFICE,
11th March 1963

DS 72296/1(3)/R.109 200 2/63 PL

be administered in a form which permits their slow and even release over relatively long periods of time.

In a previous Patent Application No. 8431/57 (Serial No. 857,193) we have described a class of new compounds and a method of obtaining slow and even release of drugs over an extended period of time under the action of the normal contents of the gastro-intestinal tract. Basically a drug is combined with an appropriate ion-exchange resin to form a compound. For example a drug of a basic nature may be combined with an oppositely-charged cationic ion-exchange resin, i.e. one which exchanges cations, to form what may be called a "resinate" of the drug, whilst a drug of an acidic nature may be combined with an anionic ion-exchange resin, i.e. one which exchanges anions, to form a "resin-drug" compound which is a salt of the resin acting as a base and the drug acting as the acid.

[*Price 3s. 6d.*]

For example, if a resinate containing a low concentration of one particular drug is administered together with a separate resinate containing another drug in a different concentration, then the rate at which the two separate drugs are released will be different, and there may then be high dosage of one medicament and low dosage of the other at one period, with a reversal at another period.

If a mixture of two or more resin-drug compounds is used and one of them is saturated by a drug and the other is unsaturated, or if the degree of saturation is different, then the unsaturated resin-drug compound or the one with a lower degree of saturation in relation to the other will act as a diluent of the saturated compound and affect the rates of release of the different drugs and their physiological availability.

It is accordingly the object of the present invention to provide improved resin-drug compounds in the form of orally administrable

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International Classification:—**A61k.**

COMPLETE SPECIFICATION

Therapeutic Agents comprising Ion-Exchange Resins

We, CLINICAL PRODUCTS LIMITED, a Body Corporate organised under the Laws of Great Britain, now of 16, Berkeley Street, London, W.1, formerly of 2, The Green, Richmond, Surrey, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to medicinal products.

It is well known in the medical art that the oral route is to be preferred generally for the administration of drugs. On the other hand not all drugs are conveniently administered in this manner, and in particular for the reason that they may be either too readily absorbed, with a consequent danger from toxic dosage, or again they may be to readily excreted and thus pass out of the body before the therapeutic effect can be realised. For this reason it is generally desirable that such drugs shall be administered in a form which permits their slow and even release over relatively long periods of time.

In a previous Patent Application No. 8431/57 (Serial No. 857,193) we have described a class of new compounds and a method of obtaining slow and even release of drugs over an extended period of time under the action of the normal contents of the gastro-intestinal tract. Basically a drug is combined with an appropriate ion-exchange resin to form a compound. For example a drug of a basic nature may be combined with an oppositely-charged cationic ion-exchange resin, i.e. one which exchanges cations, to form what may be called a "resinate" of the drug, whilst a drug of an acidic nature may be combined with an anionic ion-exchange resin, i.e. one which exchanges anions, to form a "resin-drug" compound which is a salt of the resin acting as a base and the drug acting as the acid.

[*Price 3s. 6d.*]

It is desirable in some instances to administer more than one drug at the same time, and to obtain a slow and even rate of release for each of them. The rate of release of each drug taken individually can be ascertained and is readily controllable when that drug alone is combined with a quantity of the ion-exchange resin. The rate of release can be controlled for instance by varying the proportion of drug to resin in the product. On the other hand, where several drugs are to be administered at the same time, if they are each combined with an individual quantity of resin, it is found in practice that their rates of release obtained, if the resin-drug compounds are simply mixed physically, will not be the same as if they had been administered singly. Not only will the individual rates of release vary in proportion amongst themselves, but they will also tend to be considerably slower than if each were administered alone, to an extent which may prevent their effective use. For example, if a resinate containing a low concentration of one particular drug is administered together with a separate resinate containing another drug in a different concentration, then the rate at which the two separate drugs are released will be different, and there may then be high dosage of one medicament and low dosage of the other at one period, with a reversal at another period.

If a mixture of two or more resin-drug compounds is used and one of them is saturated by a drug and the other is unsaturated, or if the degree of saturation is different, then the unsaturated resin-drug compound or the one with a lower degree of saturation in relation to the other will act as a diluent of the saturated compound and affect the rates of release of the different drugs and their physiological availability.

It is accordingly the object of the present invention to provide improved resin-drug compounds in the form of orally administrable

tablets, powders, capsules, granules or suspensions in a suitable medium such as water or oil, with which the rates of release of a plurality of drugs from the compounds can be accurately controlled.

According to the present invention, a therapeutic preparation suitable for oral administration to be acted upon by the normal contents of the stomach and gut to give a slow and even rate of release of drugs over a long period of time, comprises two or more drugs of a basic or of an acidic nature combined respectively with one quantity of a cationic or anionic exchange resin, said resin being formed from either a copolymer of styrene and containing free acidic or basic groups, or a polymerised methacrylic acid cross-linked with divinyl benzene and containing free carboxylic groups.

The term "drug" as used herein is intended to indicate any acidic or basic substances which will give a pharmacological response and which is capable of forming a complex with an anion or cation exchange resin respectively. It is to be noted that some drugs, although basic in reaction, may also contain acidic groups, e.g. certain alkaloids such as trigonelline, arecaidine and ecgonine. Further, other drugs are acidic in reaction, but also contain basic groups, e.g. nicotinic acid, folic acid and pantothenic acid.

Two or more drugs of an acidic nature may be combined with an anionic ion-exchange resin to form salts in which the resin acts as base and the drug acts as acid, or again two or more drugs of a basic nature may be combined with a cationic ion-exchange resin to form "resinates".

When one drug is combined with a resin to produce a resin-drug compound then a further separate drug can be combined with this compound to produce a further compound with the two drugs combined with the resin in the desired proportions. The simultaneous release of the two drugs will be in the same proportion in which they occur for both the resin drug compounds and the resinate compounds.

The slope of the curve depicting the amount of drug release against time may be influenced by the choice of the resin used and by varying the total concentration of the drugs in the compound when made, or by adding varying amounts of pure resin to the compound produced by saturating the resin with the drug.

Examples of "basic" drugs i.e. those with a basic reaction which may be combined in pairs or multiples in a single compound of the "resinate" type are:—

(a) basic alkaloids, such as morphine, ephedrine and atropine.
(b) basic alkaloids, containing acidic groups, such as trignelline, arecaidine and ecgonine.
Antihistamines
Basic - vitamins such as Aneurine, Pyridoxine and Riboflavine.
Derivatives of phenyl - alkylamines

Examples of "acidic" drugs i.e. those with an acidic reaction which may be combined in pairs or multiples in a single resin salt-drug acid compound are:—

Barbituric acid derivatives
Aspirin
Valerianic acid
Acidic vitamins such as ascorbic acid, nicotinic acid, pantothenic acid and folic acid.

One or more drugs of both the resinate and the resin salt-drug acid types may be mixed and used together in "multiple" compositions.

Suitable ion-exchange resins are available commercially (e.g. Zeokarb 225, Amberlite IR-120, DeAcidite F.F. or Amberlite IRA 400) and may be divided into four types according to the functional groups associated with the synthetic, insoluble, macromolecular compound known as the resin matrix. (Zeokarb, Amberlite and DeAcidite are Registered Trade Marks).

The resin matrix is usually a polystyrene in which the amount of cross-linking may be varied and the functional group is:—

(i) The sulphonic acid group (strong cationic exchange resin) e.g. Zeokarb 225 or Amberlite IR-120, or Dowex 50.

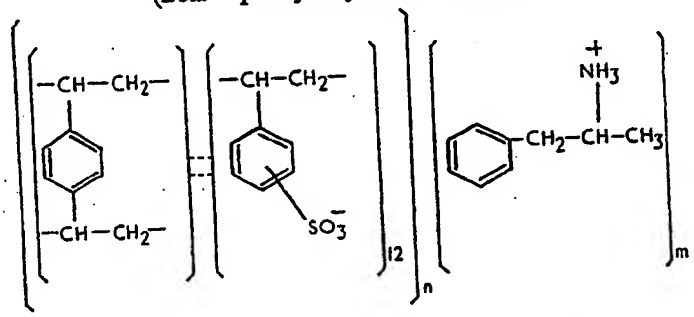
(ii) The carboxyl group (weak cationic exchange resin) e.g. Zeokarb 226, Amberlite IRC-50.

(iii) a quaternary ammonium group (strong anionic exchange resin) e.g. DeAcidite FF, Amberlite IRA-400, Dowex 1 and 2 or

(iv) the primary amino group (weak anionic exchange resin) e.g. DeAcidite E, Amberlite IR-45.

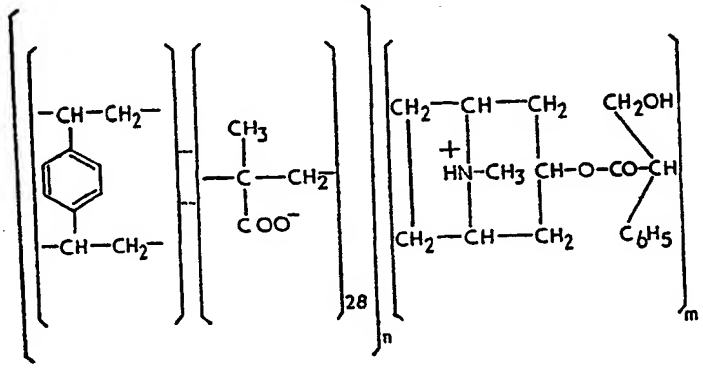
Formulae for representative compounds are given below:—

Sulphonic acid resin and dexamphetamine
(Beta - phenylethylamine derivative)



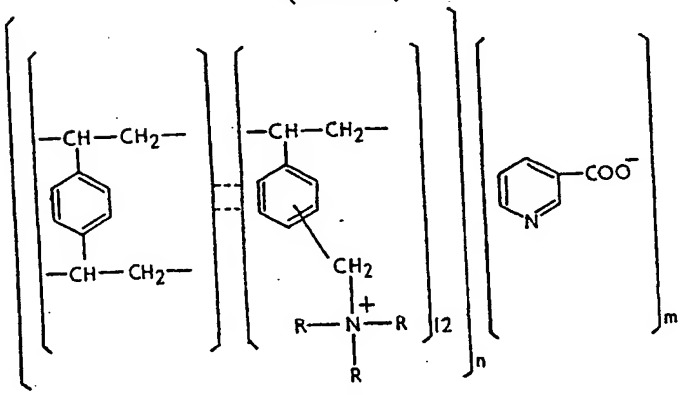
The ratio m/n represents the degree of saturation of the resin with the drug.

Carboxyl resin and hyoscyamine
(an alkaloid)



The ratio m/n represents the degree of saturation of the resin with the drug.

Quaternary ammonium resin and nicotinic acid
(a vitamin)



The ratio m/n represents the degree of saturation of the resin with the drug.

The resin containing an acidic functional group (—SO_3H) or —COOH) e.g. Zeokarb 225, Zeokarb 226, will combine with a drug containing a basic group such as alkaloids or amines e.g. Ephedrine or amphetamine whereas those containing a functional group of basic character (quaternary ammonium or primary amino) e.g. DeAcidite FF, DeAcidite E will combine with drugs of an acidic character such as acids, barbituric acid derivatives, e.g. Aspirin, amylobarbitone, phenobarbitone.

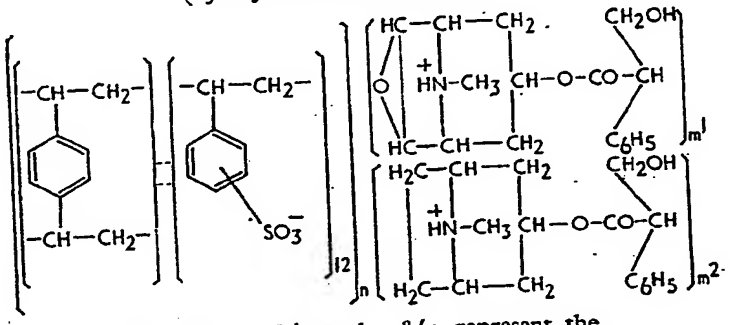
A first example of the formation of a multiple drug resinate to include Hyoscine and Hyoscyamine is given below:—

Hyoscyamine Resinate is prepared as follows:—

50 g. of a suitable sulphonic acid cross-linked polystyrene resin such as Zeokarb 225H or Amberlite IR-120 (both in the hydrogen form) is placed in a tube and a solution containing 4.4 gm. of hyoscyamine sulphate in 50 mls. of distilled water is passed through the tube until the resin has completely absorbed the drug from the solution. The amount of drug used is not sufficient to saturate the resin. Hyoscyamine/hyoscine Resinate is then prepared as follows:—

77.6 mg. of hyoscine hydrobromide is dissolved in 50 mls. of distilled water and the pH value determined. Then 7.4 grammes of the hyoscyamine resinate is added. The pH value falls over the next 15 minutes and then remains steady. The resinate is filtered and the hyoscine content of the solution is then determined, giving the amount which has reacted with the hyoscyamine resinate. The reaction is then continued until the resinate contains 0.664% by weight of hyoscine alkaloid. The resinate is then filtered off, washed successively in water, alcohol, and acetone, and dried.

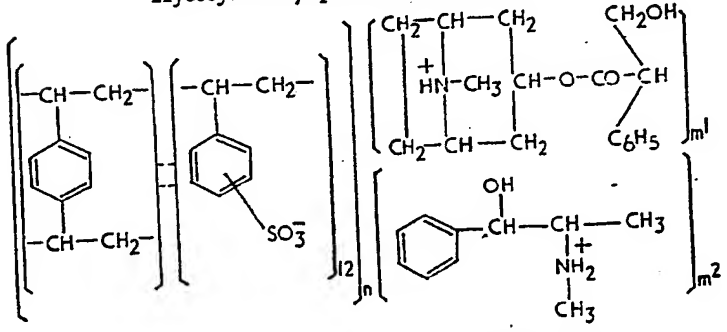
Formula of compound of a cationic ion-exchange resin plus two basic drugs (hyoscyamine and hyoscine)



The ratios m^1/n and m^2/n represent the degrees of saturation of the resin with the respective drugs.

In a second example a similar method is used but with hyoscyamine sulphate to form the resinate, and ephedrine hydrochloride utilised in place of hyoscine hydrobromide

Formula of compound:
Hyoscyamine/ephedrine resinate:



The ratios m^1/n and m^2/n represent the degree of saturation of the resin with the respective drugs.

In a third example a multiple resin-drug compound to include amylobarbitone and phenobarbitone is given below:

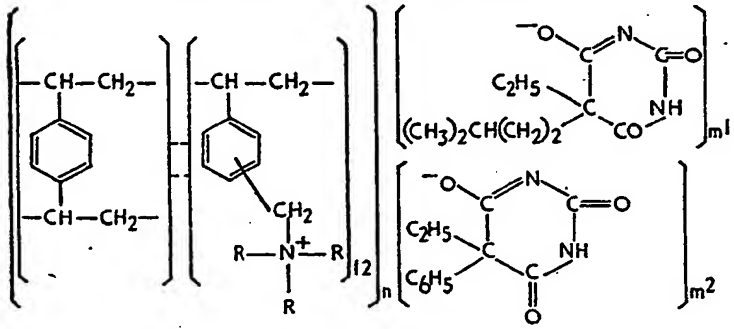
5—20% solution of sodium amylobarbitone in distilled water is prepared and reacted with an anionic ion-exchange resin such as De-Acidite F.F., in the manner described precedingly until the reaction has reached ionic equilibrium as shown by constant pH reading of the mother liquor. The reaction is repeated if necessary with fresh solution of sodium amylobarbitone until the desired concentration of barbiturate in the resin compound is obtained.

The amylobarbitone resin compound so formed is removed from the solution and washed with distilled water and alcohol.

A 5—20% solution of sodium phenobarbitone is now prepared and the amylobarbitone resin compound is added. The reaction is continued in the same manner as given above for amylobarbitone resin until the desired concentration of phenobarbitone is obtained.

The combined barbiturate resin compound is removed from the solution, washed with distilled water and alcohol and finally dried at a temperature not exceeding 60°C. until the moisture content is below 2%.

The formula of a compound of an anionic ion-exchange resin plus two acidic drugs (amylobarbitone and phenobarbitone) is:—



The ratios m^1/n and m^2/n represent the degree of saturation of the resin with the respective drugs.

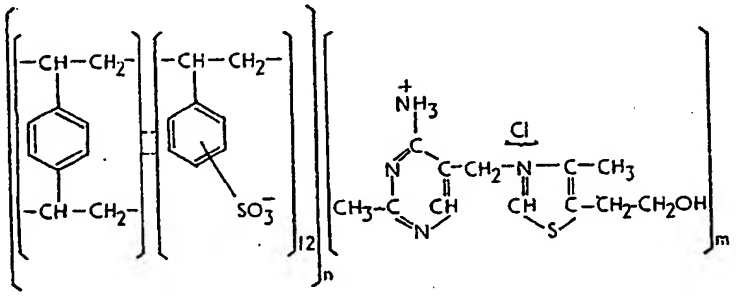
In a modification, a resin-drug compound with hyoscine and hyoscyamine is produced by agitating the pure resin firstly in a solution of hyoscyamine sulphate and thereafter in a solution of hyoscine hydrobromide. Preferably, the resin is removed from the two solutions when it has been determined that a sufficient quantity of the individual drugs has been absorbed.

In any of the above examples, the resulting resin-drug compound may be diluted with pure resin for varying the rate of release.

Where it is desired to eliminate the odour of an odoriferous drug, e.g. Valerianic acid or Aneurine, the drug may be combined with the resin to form a single resin-drug compound, e.g. resin valerianate or aneurine resinate and such a drug may form one of the pair of multiple drugs incorporated with a single resin in the manner described above and wherein its odour is eliminated as in the case of the compound of the single drug and resin.

By way of example, aneurine resinate may be prepared taking 100 mils of a 10% solution of aneurine hydrochloride, adding 5 grammes of Zeokarb 225H and stirring. The pH value is checked until it remains constant. The resinate is then filtered off, washed with water, and dried.

Formula of aneurine resinate:—



The ratio m/n represents the degree of saturation of the resin with the drug.

WHAT WE CLAIM IS:—

1. A therapeutic preparation suitable for oral administration for acting upon by the normal contents of the stomach and gut to give a slow even rate of release of drugs over a relatively long period of time, comprising two or more drugs each of which is either of a basic or of an acidic nature combined respectively with one quantity of an anionic or cationic exchange resin, said resin being formed from either a copolymer of styrene and containing acidic or basic groups, or a polymerised methacrylic acid cross-linked with divinyl benzene and containing carboxylic groups.

2. A therapeutic preparation, as claimed in claim 1, in which the quantities of drugs combined with the resin are less than that required to saturate the resin.

3. A therapeutic preparation, as claimed in claim 1, wherein the resin matrix is a polystyrene in which the functional group is a sulphonic acid group, a carboxyl group, a quaternary ammonium group, or a primary amino group.

4. A therapeutic preparation, as claimed in claim 1, wherein a cationic resin is combined with any two or more alkaloids, antihistamines, basic vitamins, or derivatives of Beta Phenylethylamine.

5. A therapeutic preparation, as claimed in claim 1, wherein an anionic resin is combined with any two or more drugs selected from barbituric acid or derivatives thereof, valerianic acid, and aspirin.

6. A therapeutic preparation, as claimed in claim 1, in which a single quantity of cationic resin is combined with hyoscine and hyoscyamine.

7. A therapeutic preparation, as claimed in Claim 1, in which a single quantity of cationic resin is combined with hyoscine and ephedrine.

8. A therapeutic preparation, as claimed in either claims 6 and 7, including additional pure cationic resin as a diluent.

9. Hyoscine - hyoscyamine resinate prepared in the manner particularly described herein.

10. Hyoscyamine - ephedrine resinate prepared in the manner particularly described herein.

11. A therapeutic preparation, as claimed in Claim 1, wherein a single quantity of the cation exchange resin is combined with two or more drugs selected from aneurine, pyridoxine and riboflavine.

CHATWIN & COMPANY,
Chartered Patent Agents,
253, Gray's Inn Road, London, W.C.1.

PROVISIONAL SPECIFICATION

Therapeutic Agents comprising Ion-Exchange Resins

We, CLINICAL PRODUCTS LIMITED, a Body Corporate organised under the Laws of Great Britain, of 2, The Green, Richmond, Surrey, do hereby declare this invention to be described in the following statement:—

This invention relates to medicinal products, and more particularly to a new drug composition and a new method for the administration of drugs.

It is well known in the medical art that the oral route is to be preferred generally for the administration of drugs. On the other hand not all drugs are conveniently administered in this manner, and in particular for the reason that they may be either too readily absorbed, with a consequent danger from toxic dosage, or again they may be too readily excreted and thus pass out of the body before the therapeutic effect can be realised. For this reason it is generally desirable that such drugs shall be administered in a form which permits their slow and even release over relatively long periods of time.

In a previous Patent Application No. 8431/57 (Serial No. 857,193), we have described a class of new compounds and a method of obtaining slow and even release of drugs over an extended period of time under the action of the normal contents of the gastro - intestinal tract. Basically an ionisable drug is combined with an appropriate ion-exchange resin to form a resin-drug compound. For example a basic therapeutic agent may be combined with an appropriate cationic ion-exchange resin to form what may be called a "resinate" of the drug, whilst an acidic therapeutic agent may be combined with an appropriate anionic ion-exchange resin to form a resin-drug compound which is a salt of the resin acting as a base and the drug acting as the acid.

It is desirable in some instances to administer more than one therapeutic agent at the same time, and to obtain a controlled rate of release for each of them. The rate of release of each agent taken individually can be ascertained and is readily controllable when that agent alone is combined with a quantity of the appropriate ion-exchange resin. The rate of release can be controlled for instance by varying the proportion of agent to resin, short of saturation, in the product. On the other hand, where several agents are to be administered at the same time, if they are each combined with an individual quantity of resin, it is found in practice that their rates of release obtained, if the resin-drug compounds are simply mixed physically, will not be the same as if they had been administered singly. Not only will the individual rates of release vary in proportion amongst themselves, but they will also tend to be considerably slower, to

an extent which may prevent their effective use. For example, if a resinate containing a low concentration of one particular drug is administered together with a separate resinate containing another drug in a different concentration, then the rate at which the two separate drugs are released will be different, and there may then be high dosage of one medicament and low dosage of the other at one period, with a reversal at another period.

If a mixture of two or more resinates is used and one resinate is saturated by a drug and the other resinate is unsaturated or the saturation ratio of the drugs is different then the unsaturated resinate or the one with a lower saturation ratio in relation to the other drug or drugs will act as a diluent of the saturated resinate and affect the rates of release of the different drugs and their physiological availability.

It is accordingly a first object of the present invention to provide improved resin-drug compounds and a method of administering such drugs, whereby the rates of release of a plurality of drugs can be accurately controlled.

It is known in the medical art that certain drugs have a distinctive odour which is in some cases exremely objectionable and which seriously hinders the capabilities of use of the drug due to the reluctance of the patient to take it. A second object of the present invention is accordingly to provide improved therapeutic products in which a drug normally having an odour is chemically combined in such a manner as to lose its odour during the combined state but without the loss of its inherent therapeutic properties.

According to the present invention, two or more therapeutic agents are combined with a single quantity of an appropriate ion-exchange resin to form resin-drug compounds, either of the "resinate" or resin-salt/drug-acid type, according to the nature of the drug.

When one drug is combined with a resin to produce a resinate, then a further separate drug can be combined with this resinate to produce a resinate with the two drugs combined in the correct proportion, it being understood that only two or more basic or two or more acidic drugs are used. The release of the two drugs will be simultaneously in the same proportion in which they occur in the resinate.

If two basic or acidic medicinal substances are combined with the appropriate resin and the two substances concerned have different strengths as bases or acids the appropriate percentage composition can be varied to obtain a given rate of release of each individual substance.

The rate of release of the two or more medicaments from a complex resin drug compound may be controlled by combination of a second, third or more drugs in rotation onto a primary drug resinate.

The shape of the curve depicting the amount of drug release against time may be influenced by the choice of the resin used and by varying the total concentration of the drugs in the compound resinate when made or by adding varying amounts of pure resin to the compound produced by saturating the resin with the drug.

Examples of drugs which it may be desirable to combine in pairs or multiples in a single resin-drug compound of the "resinate" type are:—

Alkaloids
Antihistamines
Vitamins such as Aneurin
Derivatives of Beta phenylethylamine
Medicinal compounds of a basic nature.

Examples of drugs which it may be desirable to combine in pairs or multiples in a single resin-drug compound of the resin-salt/drug-acid type are:—

Barbituric acid derivatives
Aspirin
Valerianic acid
Medicinal compounds of an acidic nature.

One or more drugs of both types may be included together in a multiple resin-drug compound.

Suitable ion-exchange resins are available commercially (e.g. Zeocarb 225, Amberlite IR-120, DeAcidite F.F. or Amberlite IRA) and may be divided into four types according to the functional groups associated with the synthetic, insoluble, macromolecular compound known as the resin matrix.

The resin matrix is usually a polystyrene in which the amount of cross-linking may be varied and the functional group is:—

(i) The sulphonic acid group (strong cationic exchange resin) e.g. Zeocarb 225 or Amberlite IR-120, or Dowex 50.

(ii) The carboxyl group (weak cationic exchange resin) e.g. Zeocarb 226, Amberlite IRC-50.

(iii) a quaternary ammonium group (strong anionic exchange resin) e.g. DeAcidite FF, Amberlite IRA-400, Dowex 1 and 2 or

(iv) the primary amino group (weak anionic exchange resin) e.g. DeAcidite E. Amberlite IR-45.

The resin containing an acidic functional group (—SO_3H) or —COOH) e.g. Zeocarb 225, Zeocarb 226, will combine with a therapeutic agent containing a basic group such as alkaloids or amines e.g. Ephedrine or amphetamine whereas those containing a functional group of basic character (quaternary ammonium or primary amino) e.g. DeAcidite FF, DeAcidite E will combine with therapeutic agents of an acidic character such as

acids, barbituric acid derivatives, e.g. Aspirin amylobarbitone, phenobarbitone, etc.

A first example of the formation of a multiple resin/resinate to include Hyoscine and Hyoscyamine is given below:—

Hyoscyamine Resinate is prepared as follows:—

A quantity of a suitable sulphonic acid cross-linked polystyrene resin such as Zeocarb 225H or Amberlite IR-120 (both in the hydrogen form) is placed in a tube and a solution of hyoscyamine sulphate is passed through the tube until the resin has completely absorbed the drug from the solution. The amount of drug used is not sufficient to saturate the resin. 77.6 mg. of hyoscine hydrobromide is then dissolved in 50 ml. of distilled water, and the pH value determined. Then 7.4 grammes of the hyoscyamine resinate are added. The pH value falls over the next 15 minutes and then remains steady. The resinate is filtered and the hyoscine content of the solution is then determined, giving the amount which has reacted with the hyoscyamine resinate. The reaction is then continued until the resinate contains 0.664% of hyoscine alkaloid. The resinate is then filtered off, washed and dried.

In a second Example, a similar method is used but with hyoscyamine sulphate to form the resinate, and ephedrine hydrochloride utilised in place of hyoscine hydrobromide.

In a third example, suitable salts of amylobarbitone and phenobarbitone are treated in similar manner.

In a modification, a multiple resin-drug compound with hyoscine and hyoscyamine is produced by agitating the pure resin firstly in a solution of hyoscyamine sulphate and thereafter in a solution of hyoscine hydrobromide. Preferably, the resin is removed from the two solutions when it has been determined that a sufficient quantity of the individual drugs has been absorbed.

In any of the above examples, the resulting multiple resin-drug compound may be diluted with pure resin for varying the in vitro rate of release.

Where it is desired to eliminate the odour of an odoriferous drug, e.g. Valerianic acid or Aneurin, the drug may be combined with the resin to form a single resin-drug compound, e.g. resin valerianate or aneurine resinate. Such a drug may also form one of the pair of multiple drugs incorporated with a single resin in the manner described above.

By way of example, aneurine resinate may be prepared taking 100 mils of a 10% solution of aneurine hydrochloride, adding 5 grammes of Zeocarb 225H and stirring. The pH value is checked until it remains constant. The resinate is then filtered off, washed with water, and dried.

Resin valerianate may be prepared in similar manner, using a 10% solution of valerianic acid and DeAcidite F.F. (in the chloride form) as the starting materials, the quantities being the same.

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Chartered Patent Agents,
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